

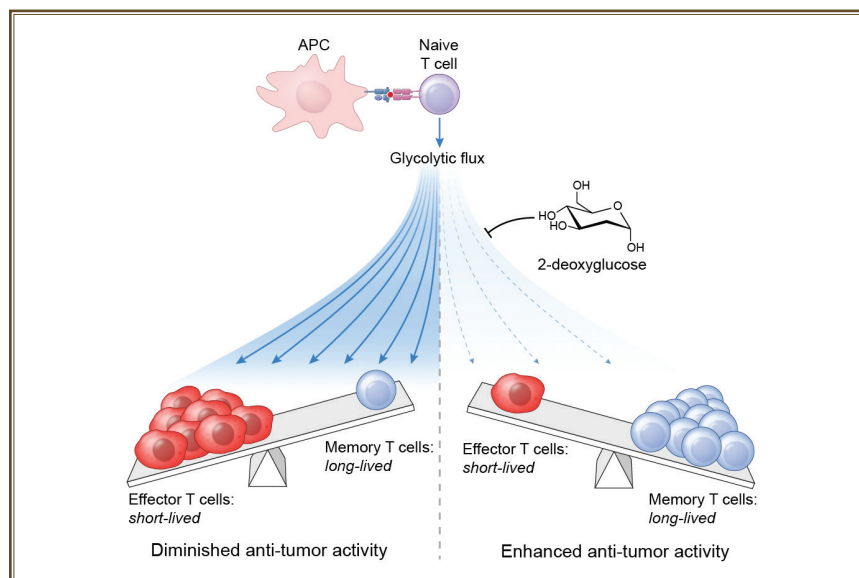
A Bias for Memory

Manipulating glucose metabolism predictably alters T-cell phenotypes.

Luca Gattinoni, M.D., Earl Stadtman Tenure-Track Investigator in CCR's Experimental Transplantation and Immunology Branch, has a rather straightforward goal for his research: to design better immunotherapies for cancer. In particular, he focuses on the adoptive transfer of T cells, naturally strong defenders against tumors that become exhausted and subverted as cancers progress. When primed with a tumor antigen, T cells are stimulated to produce two classes of cells: memory cells that live to fight another day and effector cells that immediately seek out and destroy their foes. The long-term success of adoptive transfer depends on the proportion of memory T cells. In the *Journal of Clinical Investigation*, Gattinoni, Nicholas Restifo, M.D., in CCR's Surgery Branch, and their colleagues show that they can bias this proportion by making systematic adjustments to cellular metabolism.

More than 50 years ago, Nobel laureate Otto Warburg first noted that, in contrast to normal cells, cancer cells employ glycolysis to generate the energy needed for cellular growth even in the presence of oxygen. Similar metabolic changes occur in T cells following activation. While quietly patrolling for specific miscreants, T cells rely on aerobic fatty acid oxidation to fulfill their energy requirements. However, when faced with the need to proliferate and differentiate, their metabolism is diverted towards glycolysis, which generates a number of biosynthetic intermediates that are required by growing cells.

Given this background, Gattinoni and his team asked whether the switch from fatty acid oxidation to glycolysis is an adjustment the cell makes once its fate is sealed or whether the switch might in fact contribute to the cell's fate *in vivo*. To address this question, first they monitored glucose metabolism



(Image: L. Gattinoni, CCR)

After encountering antigen, naïve CD8⁺ T cells undergo an extensive period of proliferation and expansion, and differentiate into effector cells and distinct memory T cell subsets. Increasing glycolytic flux pushes CD8⁺ T cells towards a terminally differentiated state that diminishes antitumor activity. In contrast, inhibiting glycolysis using 2-deoxyglucose (2DG) maintains the formation of long-lived memory CD8⁺ T cells and enhances antitumor activity.

in T cells with a fluorescent probe before injecting them into mice and challenging them with a pathogenic signal. They separated the T cells into low and high glucose metabolizers and found that the mice injected with low glucose metabolizers were much more effective in mounting an immune response when challenged several weeks later. In parallel, they saw that the low and high glucose metabolizers displayed gene expression signatures that aligned with memory and effector cells, respectively.

The next logical question was whether altering glycolysis could influence T cell effectiveness. To manipulate the glycolytic pathway, Gattinoni and his colleagues used overexpression of the enzyme phosphoglycerate mutase-1 to show that genetically enforced glycolysis was sufficient to bias the population towards effector phenotypes and reduce the strength of the immune response over time. Inhibition of glycolysis with 2-deoxyglucose had

the opposite effect, increasing the population of memory T cells and the concomitant response to immunologic challenge.

Taken together, this work suggests strategies to increase the therapeutic efficacy of adoptive T cell transfer by biasing the population towards a memory response. Because cancer cells also have a heightened glucose metabolism, clinical strategies are already under development to inhibit this pathway in cancer cells, which might be extrapolated to the immune system. "Modulation of the metabolism of the antitumor T cell response could be an important addition to the immunotherapist's armamentarium," concluded Gattinoni.

To learn more about Dr. Gattinoni's research, please visit his CCR Web site at <http://ccr.cancer.gov/staff/staff.asp?name=Gattinoni>.